AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph at page 11, lines 16-17 with the following paragraph:

~~Figure 3 is a diagram~~ Figures 3A and 3B are diagrams illustrating the object representation of molecules and relations between them;

Please replace the paragraph at page 12, lines 10-12 with the following paragraph:

~~Figure 6 shows~~ Figures 6A and 6B show the original tree of ALDH sequences, indicating sequence clusters where bacterial, plant, fungal and nematode orthologous genes are present, but a human ortholog was not yet known;

Please replace the paragraph at page 12, lines 13-15 with the following paragraph:

~~Figure 7 shows~~ Figures 7A and 7B show the same phylogenetic tree as in ~~Figure 6~~ Figures 6A and 6B with an additional human protein, referred to as antiquitin which was discovered by the method of the invention;

Please replace the paragraph at page 13, lines 19-22 with the following paragraph:

~~Figure 13 Identification~~ Figures 13A-C show the identification of genes in *C. elegans* containing either POZ or kelch domains. The protein excession numbers are indicated adjacent to the different protein domains. The protein corresponding to accession number gi/1132541 contains a POZ domain, death domain, kinase domain and heat repeat.

Please replace the paragraphs beginning at page 37, line 7 and ending at page 38, line 17 with the following paragraphs:

In addition, in yet another embodiment of the invention, a specialized database may be designed to contain a semantic model of proteins and of the possible interactions between them. Such databases are particularly useful for computation and analysis of regulatory networks between proteins. The semantic model is designed for representing substances, such as proteins and actions between them, and is based on widely accepted principles of object-oriented programming languages such as Java. ~~Figure 3 is a diagram~~ Figures 3A and 3B are diagrams illustrating the object representation of molecules and relations between them. As indicated in ~~Figure 3~~ Figures 3A and 3B there are six major classes, corresponding to the top-level classification of objects and actions: (*i*) a substance; (*ii*) a state of a substance; (*iii*) a similarity between substances; (*iv*) an action between substances; (*v*) a result of the action; and (*vi*) a mechanism that enables an action.

~~Figure 3 presents~~ Figures 3A and 3B present the class design graphically, listing the variables that represent the properties of each class or class object in the implementation. Classes can be made nested via the mechanism of "inheritance", *i.e.*, classes are defined starting with the most general ones and moving towards more specific classes. Definition of more specific classes is simplified because the properties of the general classes are "inherited" by the specific classes and need not be redefined each time (see, Flanagan 1997, Java in a Nutshell, Second Edition. O'Reilley & Associates, Inc. Sebastopol, CA).

As shown in ~~Figure 3~~ Figures 3A and 3B, the two key object types in this scheme are substances (nodes of the graph representing regulatory networks) and actions (oriented edges

connecting pairs of nodes), while result and mechanism objects are auxiliary to object action. Each substance object is characterized with a state. In this scheme, action is the most complicated object; each action object is characterized by a specific pair of substances participating in the action, one of which can be active and is referred to as Subject Substance and the second of which can serve as a substrate for the former and is referred to as Object Substance. Furthermore, for each action the initial and final states corresponding to interacting substances are defined. The property Time Required of each Action Object allows the setting of different durations for different actions (time is measured in relative units; see René Thomas and Richard D'Ari, 1990, "Biological Feedback," CRC Press Boca Raton, Ann Arbor, Boston).

Please replace the paragraph at page 47, lines 9-15 with the following paragraph:

The aldehyde dehydrogenase gene cluster is highlighted in ~~Figure 6~~ Figures 6A and 6B which ~~shows~~ show the original tree of ALDH sequences, the circled area indicating a sequence cluster where bacterial (*Bacillus subtilis*), plant (*Brassica napus*), and nematode (*Caenorhabditis elegans*) ortholog is present, but a human ortholog is not known. A random screening of cDNA libraries showed that a human ortholog, referred to as antiquitin, does exist. ~~Figure 7 shows~~ Figures 7A and 7B show the same gene tree as in ~~Figure 6~~ Figures 6A and 6B with an additional human protein referred to as antiquitin present in the tree.

Please replace the paragraph at page 66, lines 3-14 with the following paragraph:

Identification of a putative apoptosis-related human gene began with an identification of all genes in *C. elegans* that contained either a POZ or kelch domain. A subset of

these genes is shown in ~~Figure 13~~ Figures 13A-13C. Hidden Markov Models (HMM) for the POZ and Kelch domains were built as follows. Starting with POZ and kelch sequences from the *Drosophilia* kelch protein (gi | 577275) homologs were identified in other protein sequences using the BLASTP program. The resulting sequences showing significant similarity (e-value less than 0.001) were aligned using CLUSTALW program and the alignments were used to build Hidden Markov Models with HMMER-2 package (Krogh et al., 1995, :http://hmmer.wustl.edu/). A computer printout listing of HMM models of tumor suppressors appears as a Microfiche H to the present specification. (See, http://hmmer.wustl.edu; Chapter 2, which is incorporated by reference herein in its entirety, for a detailed description of HMM models).

Please replace the paragraph at page 67, lines 1-6 with the following paragraph:

One of the unannotated protein-coding genes of *C. elegans* (corresponding protein accession number gi | 1132541, see ~~Figure 11~~ Figures 11A-11B) appeared to include a POZ domain, death domain, kinase domain, and heat repeat. A death domain is characteristic for the apoptosis system and a kinase domain indicates that the protein is likely to participate in phosphorylation of other proteins. The presence of these particular domains suggests that this protein is serving as a regulatory protein.

Please replace the paragraph beginning at page 68, line 15 and ending at page 69, line 7 with the following paragraph:

Genomic and cDNA sequences located in the region of human chromosome 13q were compared with the Apoptosis3 database using BLASTALL program from BLAST program

complex. This region of the human genome is associated with Chronic Lymphocytic Leukemia (CLL). The comparison revealed significant similarity between a CLL region open reading frame and the mouse RPT1 protein (sp|P15533|RPT1) (~~Figure 13~~ Figures 13A-C). Analysis of regulatory functions of RPT1 in the mouse reveals that this gene functions as a repressor of the interleukin 2 receptor (IL-2R) gene. When the RPT1 gene is knocked out, the regulatory effect is manifested as a block of the apoptotic pathway in T lymphocytes resulting in an accumulation of T lymphocytes in blood. This result is consistent with aberrations observed in CLL, namely abnormal accumulation of B-cells in the blood (Trentin L. et al., 1997, Leuk. Lymphoma 27:35-42) and mutations in the human RPT1 gene play a role in development of CLL.

AMENDMENTS TO THE DRAWINGS

The attached twenty-seven (27) sheets of drawings includes changes to Figures 3, 6, 7, 11, 13, and 16. These sheets replace the originally submitted set of drawings. Annotated sheets for Figures 3, 6, 7, 11, 13, and 16 show the changes made as discussed in the Remarks.

Attachment: Twenty-seven replacement sheets
Six annotated sheets showing changes for Figures 3, 6, 7, 11, 13, and 16.